App. No. 10/526,858
Office Action Dated April 27, 2009

REMARKS

Reconsideration is respectfully requested in view of the above amendments and following remarks. Claim 27 is amended and supported in Applicants' experimental results, and claims 15 and 16 are amended to be consistent with the revisions of claim 27. No new matter has been added. Claims 15, 16, and 27 are pending.

Applicants appreciate the Examiner's courtesy in interviewing this application with Applicants' representative on October 14, 2009. In the interview, an amendment was proposed to limit the combination of compounds for administration to cisplatin and (E)-4-[2-[2-[N-acetyl-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide or its pharmaceutically acceptable salt, and the issue of unexpected results was discussed. The Examiner and her Supervisor appeared to agree that the proposed amendment would advance prosecution, but that the Examiner would need to further study the unexpected results issue and update her search. No formal agreement was made, and Applicants respectfully submit the amendment and remarks herein for further consideration, along with a Request for Continued Examination.

Claims 15, 16, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hidaka et al., (US 5,972,976) in view of Goodman and Gilman (1996), and Ragaz et al. (1997). Applicants respectfully traverse the rejection for at least the following reasons.

Claim 27 is directed to a method for treating at least one malignant tumor selected from the group consisting of blood cancer, leukemia, human colon adenocarcinoma, gastrointestinal cancer, lung cancer, breast cancer, and prostate cancer. The method comprises administering a therapeutically effective amount of (E)-4-[2-[2-[N-acetyl-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide or a pharmaceutically acceptable salt thereof in combination with cisplatin, wherein the therapeutically effective amount of (E)-4-[2-[2-[N-acetyl-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide with cisplatin gives a synergistic inhibitory effect.

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The rejection states that one of ordinary skill in the art would have been motivated to combine a known anticancer drug employed in the treatment of breast cancer with the newly found drug that is capable of treating the same type of disease via a different mechanism in terms of a combination of Hidaka et al. with Goodman and Gilman, and Ragaz et al.. The rejection also questions whether synergism is present rather than an additive effect.

Applicants respectfully disagree with the conclusions made in the Office Action, and that claim 27 is obvious. For at least the reasons below, Applicants respectfully submit that their method provides unexpected results, in that one of skill in the art would not have an expectation of therapeutic synergism of a combination of each of the claimed six compounds with cisplatin, based on any combination of Hidaka et al., Goodman and Gilman, and Ragaz et al.

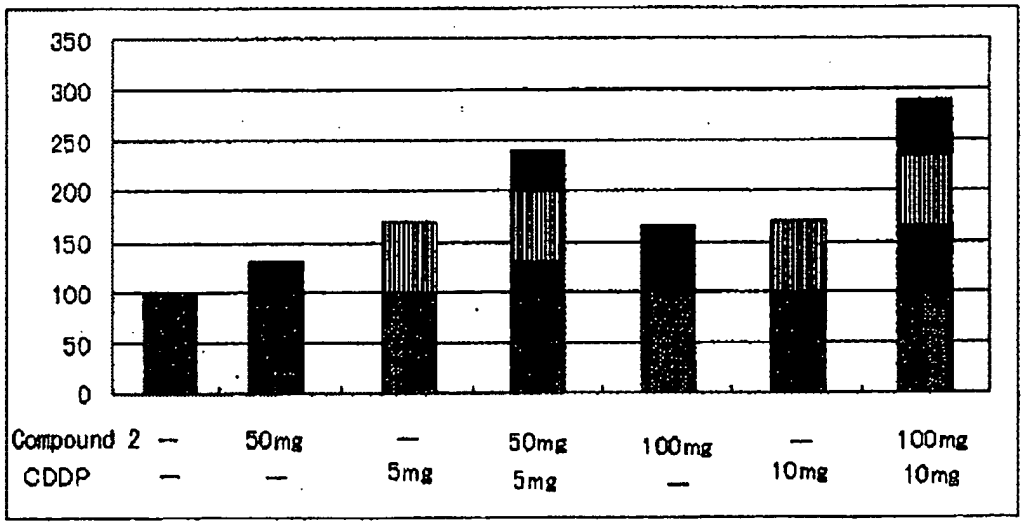
As recited by claim 27, cisplatin is used in a treatment method, which Applicants have clearly demonstrated as having a synergistic inhibitory effect in combination with (E)-4-[2-[2-[N-acetyl-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide (referred to as "Compound 2", see e.g. page 20, line 15 of Applicants' specification as filed). Table 1 of the specification reports such synergistic inhibitory effect, which was also acknowledged in the Office Action of August 18, 2008. Particularly, Table 1 reports T/C values showing that the inhibitory effect is synergistic, and not merely additive, which is further explained below.

T/C value is an indicator that shows how long survival times of animals of a treated group are extended compared to those of a control group. More precisely, a T/C value is calculated as follows: T/C = (a median survival time (MST) of a treated group/MST of a control group) x 100.

For example, in case that a MST of a treated group is 11 days and a MST of a control group is 10 days, T/C = 11/10 x 100 = 110 (%). In other words, the survival advantage from drug administration is 10%. As shown in Table 1, the T/C value in administering only Compound 2 ((E)-4-[2-[2-[N-acetyl-N-[(p-methoxyphenyl)-sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide; 50 mg) is 130%, and this means a survival advantage is 30%. The T/C value in administering only CDDP (5 mg) is 170%,

and that means a survival advantage is 70%. The additive effect therefore would be the sum of the 30% and 70% survival advantages, which is 100% expected survival advantage. However, when the compounds were combined for administration at the same dosages (Compound 2 at 50mg and CDDP at 5mg), the T/C value was reported as 240%, which is 140% expected survival advantage and clearly more than the additive effect (at least 40% more).

To further clarify such unexpected results, Applicants respectfully provide the following graph, which shows T/C values compiled from the original results reported in Table 1 of the specification of record. The graph shows T/C values of a single administration of Compound 2 (at 50 mg and at 100 mg) and a single administration of CDDP (at 5 mg and at 10 mg), and shows a combined administration of Compound 2 (50 mg) with CDDP (5 mg), and a combined administration of Compound 2 (100 mg) with CDDP (10 mg).



A sum of each survival advantage obtained in each single administration of two drugs may be considered to show an expected survival advantage of a combined administration of the two drugs, i.e. an additive effect. Meanwhile, a survival advantage is considered to be synergistic, not additive, when a survival advantage value obtained in a combined administration of two drugs is larger than a sum of each survival advantage

value obtained in each single administration of the two drugs. Applicants have clearly shown a synergistic effect based on their original disclosure.

As shown above, if the single administrations of Compound 2 (at 50 mg) and CDDP (at 5 mg) are combined (i.e. additive result), the expected survival advantage would be 100% (30% for Compound 2 + 70% for CDDP). However, as shown in Table 1 and the above graph, the actual T/C value in a combined administration of the two drugs is 240%. This means the survival advantage of the combined administration is 140%. The survival advantage (140%) is clearly larger than the expected value (100%), and hence, the advantage is synergistic, rather than additive. Similarly, the survival advantage of a combined administration of Compound 2 (100 mg) with CDDP (10 mg) is 190%, which is larger than the expected value 135% (65% for Compound 2 + 70% for CDDP). Thus, Applicants have shown that combined administration as claimed has an advantageous, synergistic effect that goes well beyond an additive effect. The references cited, however, provide neither a suggestion, nor any expectation of success for one of skill in the art to arrive at the benefits of the invention of claim 27.

Accordingly, it is clear that cisplatin in a combined administration with (E)-4-[2-[2-[N-acetyl-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine 1-oxide show a synergistic effect, as required by claim 27, and those skilled in the art would not have arrived at the advantageous effects of claim 27 based on Hidaka et al., Goodman and Gilman, Ragaz et al. Consequently, claim 27 and its dependent claims 15 and 16 are patentable over Hidaka et al., Goodman and Gilman, and Ragaz et al.

Moreover, while Goodman and Gilman disclose that cisplatin is effective as an antitumor agent (Table X-1) and while Hidaka et al. disclose the compound 2 (Example 57), there is no suggestion in the art of record to select the particular compounds for administration as claimed by Applicants' method. For at least the foregoing reasons, the references fail to teach or suggest the method of claim 27.

Favorable reconsideration and withdrawal of the rejection are respectfully requested.

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In view of the above amendments and remarks, Applicants respectfully request favorable reconsideration of this application in the form of a Notice of Allowance. If any questions arise regarding this communication, the Examiner is invited to contact Applicants' representative listed below.

Respectfully submitted,

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